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Filing Date	Feb 8, 2002
First Named Inventor	Paul Ni
Art Unit	1647
Examiner Name	L. Spector
Attorney Docket Number	TNX98-03-01

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Request for Oral Hearing

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Tanox, Inc.		
Signature	Cheryl A Liljestrand		
Printed name	Cheryl A Liljestrand		
Date	June 28, 2007	Reg. No.	45,275

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: Ni, Paul et al.	
Serial No.: 10/071,962	Group Art Unit: 1647
Filed: February 8, 2002	Examiner: L. Spector
For: G-CSF RECEPTOR AGONIST ANTIBODIES AND SCREENING METHODS THEREFOR	

REPLY BRIEF

Applicants hereby submit a Reply to the Examiner's Answer mailed May 4, 2007. This Brief is being filed within the two month period for reply. Should any fees be necessary, please charge our deposit account 20-0087.

I. Status of the Claims

On July 7, 2006, appellant appealed from the final rejection of claims 31-33, 36-38, 40, 45 and 48-50, claims 1-30, 34-35, and 42-43 having been cancelled, and claims 44, 46-47 having been withdrawn from consideration pursuant to a restriction requirement. Claims 39 and 41 are objected to for depending from rejected claims.

Claims 31-33, 36-38, 40, 45 and 48-50 are currently being appealed.

II. Grounds for Rejection to be Reviewed on Appeal

A. Claims 31-33, 36-38, 40, 45 and 48-50 have been rejected under 35 U.S.C. §102(b) as anticipated by Cunningham et al. (U.S. Pat. No. 5,506,107).

B. Claims 31-38, 40 and 45 have been rejected under 35 U.S.C. §102(b) as anticipated by Adams et al. (U.S. Pat. No. 6,342,220).

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III. Arguments In Support of Patentability In Response to Examiner's Answer

A. Claims 31-33, 36-38, 40, 45 and 48-50 have been rejected under 35 U.S.C. §102(b) as anticipated by Cunningham et al. (U.S. Pat. No. 5,506,107).

In Section 9, page 4, of the Examiner's Answer the Office states:

> Thus, Cunningham clearly not only discloses **having** such antibodies, but that they were already available in the prior art. The Examiner notes that determination of a property of a compound that was already known does not make the compound newly patentable, as a compound and its properties are inseparable.

Applicants respectfully disagree with the Office's interpretation of the Cunningham reference and the application of the law regarding known compounds. In this instance, the Appellants are not the determining of a new property of an already existing compound. No one had made agonist G-CSF antibodies prior to the filing of our application. Cunningham et al. are discussing the making of **"hGH receptor"** antibodies, not G-CSF Receptor agonist antibodies. Therefore, Cunningham is not disclosing "having" G-CSF Receptor agonist antibodies and G-CSF Receptor agonist antibodies were not available to the public prior to the filing of the present application. The Office also states at page 4:

> Thus, Cunningham discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims, and that such methods were successful in obtaining said antibodies. Accordingly, Cunningham et al. is clearly anticipatory, and fairly placed the claimed invention in the hands of the public.

Applicants again point out that the desirability of making a compound does not enable the compound. If merely listing compounds could suffice as a disclosure, it would bar patent protection to the person who actually discovered a compound on the list and, in so doing, thwart the Constitutional purpose of the patent system. See *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973), where the CCPA stated:

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> The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference.
>
> If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be. In view of the fact that the purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute.

Id. at 543, 179 U.S.P.Q. at 425 (footnote omitted).

Thus, in this case, the mere listing of a variety of cytokines to which one "might" generate an agonist antibody using a method that is unpredictable thwarts the Constitutional purpose of the statute.

In this case, the Applicants have shown that the method of screening for agonist antibodies taught by Cunningham does not work for G-CSF. As argued in previous responses to the Office's rejection, the screening assay used by Cunningham to identify agonists was discussed in the reference by Schneider as being unpredictable. These authors observed that MoAb34 appeared to be agonistic in an assay measuring ^{3}H-thymidine incorporation using artificial cell lines (figure 3B), but in the colony formation assay using human CD34^{+} cells reported in Table 2, this MoAb showed essentially no agonist activity. These same authors posed and answered the question "Why are agonist antibodies to EPO-R so rare?" The authors predicted, as Cunningham postulated, "all MoAbs specific to the extracellular domain should dimerize the receptor because they are bivalent." (page 480, last paragraph.) However, 47 out of 48 of their antibodies were not agonists. Prior to this, the authors stated, no agonist

antibodies of EPO-R had been described. They concluded that the reason that so few agonists could be isolated was that the "cell surface imposes steric constraints and the two receptor subunits in the 2:1 complex have to be at a specific orientation and/or distance relative to each other."

The same unpredictability of this screening assay was observed by the present inventors. Figure 5B of our application, MAb174-12 (solid triangles) appears to be an agonist antibody based on the amount of uptake of MTT as compared to the native G-CSF (solid squares). However, when this same antibody was tested in a colony-formation assay using human bone marrow cells as taught in Example 9 of the present application (an assay that more closely mimics a true environment of cells with native human G-CSF receptor), it showed no agonist activity. This clearly shows that there is a substantial difference between an artificial cell-line expressing a recombinant receptor and cells with an endogenous receptor. Thus, this is assay is not sufficiently predictive of agonist antibodies in a screen given the rarity of such antibodies.

In reply to Appellants arguments of the Appeal Brief the Office states in section 10, page five, of the Examiner's Answer that:

a) The Cunningham reference actually obtained the claimed antibodies, and is an anticipatory reference. Accordingly, arguments as to how hard it *might* be to obtain the antibodies and the unpredictability of doing so are not pertinent.

Appellants respectfully point out that Cunningham et al did not obtain the claimed antibodies, they made hGH receptor antibodies. Unpredictability of making the compound is relevant to the issue of whether a prior art reference is enabling for the compound being alleged as anticipated.

The Office then states:

b) The Schneider paper I) is not the closest prior art, as it is not related to G-CSF itself, but to EPO, the receptors for which are quite distinct, II) Schneider et al. actually obtained an agonist antibody, out of 48 screened (according to appellant's characterization of the paper), clearly demonstrating that it did not require undue experimentation to find such antibodies.

Appellants are not arguing that Schneider is the closest prior art. The Schneider reference was cited as evidence that making agonist antibodies to this cytokine family is unpredictable and not routine as the Office alleges. EPO receptor is in the same family of compounds as hGH receptor, to which Cunningham made antibodies.

Unpredictability of the assay taught by Cunningham for identifying an agonist GCSF Receptor antibody, the fact that Cunningham merely lists making agonists to G-CSF and did not actually make any G-CSF agonist antibodies, and the fact that it is difficult to make agonist antibodies to this family of receptors makes Cunningham non-enabling prior art. In view of the fact that Cunningham is not valid prior art, the Office made a clear error in rejecting the claims as anticipated, and Appellants request that the rejection be reversed.

As to the statements regarding Claim 49, Appellants respectfully point out that limitations of claim 49 necessarily make it narrower in scope than claim 31. Even though the claim language includes the phrase "a functional variant of SEQ ID NOs 15-20", one must start with the sequences taught by the Appellants. Cunningham does not teach these sequences, or the antibodies of mAB 166-93 or mAB174-24-11.

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B. Claims 31-38, 40 and 45 have been rejected under 35 U.S.C. §102(b) as anticipated by Adams et al. (U.S. Pat. No. 6,342,220).

In this rejection, the Office again points to a laundry list of compounds to which one might make an agonist antibody Col. 12, line 54, reproduced in the Examiner's answer at page 7. The Office relies on Cunningham to support the assertion that it was routine to make these antibodies. For all of the reasons discussed in Section A of this Reply Brief and those arguments made in the Appeal Brief, making agonist antibodies to cytokine superfamily members was not routine at the time of filing. Adams et al. do not make any G-CSF agonist antibodies either. The Adams patent disclosure and claims are directed to anti-thrombopoetin (c-mpl) antibodies.

Unpredictability of the assay taught by Cunningham for "how to make", the fact that Adams et al. merely lists making agonists to G-CSF and did not actually make any G-CSF agonist antibodies, and the fact that it is difficult to make agonist antibodies to this family of receptors makes Adams non-enabling prior art. In view of the fact that Adams is not valid prior art, the Office made a clear error in rejecting the claims as anticipated, and Appellants request that the rejection be reversed.

C. Summary

For the foregoing reasons, Appellant believes that the Office's rejection of claims 31-33, 36-38, 40, 45 and 48-50 were erroneous, and reversal of these rejections is respectfully requested.

Respectfully Submitted

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